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Efficacy and treatment costs of Zoledronate versus Pamidronate in Paediatric Osteoporosis

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Abstract:

Intravenous pamidronate has been used in the treatment of osteogenesis imperfecta (OI) in children for over 20 years. The more potent zoledronate is an attractive alternative as it is administered less frequently. This study compares the clinical efficacy of intravenous pamidronate (1.5mg/kg/day over 2 days, 3-monthly) vs zoledronate (0.05mg/kg/dose 6-monthly) in 40 children (20 per group) with mild to moderate OI, and the treatment costs of the two drugs in a tertiary centre for children with osteoporosis. Lumbar spine bone mineral density and fracture rate did not differ between drug groups following 1 and 2 years of treatment, respectively. Total cost per treatment course per patient was £1157 for pamidronate and £498 for zoledronate. Therefore zoledronate is a considerably cheaper alternative to pamidronate with comparable efficacy, resulting in substantial annual savings for health care providers, and a more convenient option for patients due to fewer hospital visits.

Introduction:

Osteogenesis imperfecta (OI) is an inheritable connective tissue disorder resulting from quantitative or qualitative defects in type I collagen. OI is characterised by low bone mass with high material density, resulting in increased bone fragility. Children often present with low trauma fractures, some of which heal with residual bony deformities.[1] Management of OI in children includes a multi-disciplinary approach aiming to reduce fracture risk and improve functional outcomes.

Bisphosphonates, synthetic analogues of pyrophosphate, are widely used in the management of OI in children. Their main function is to inactivate osteoclasts, resulting in reduced bone resorption, which facilitates cortical and trabecular bone thickening, increased bone mass and reduced fracture risk. [2] Intravenous Pamidronate is the most widely used bisphosphonate in children, traditionally administered over 2-3 days, 4 times per year. [3] Zoledronate, a more potent nitrogen-containing bisphosphonate is an attractive alternative as it can be administered at lower doses, much shorter infusion times and less frequently. The side effect profile of zoledronate is similar to pamidronate. [4 5]

Very little information is available on how efficacy compares between pamidronate and zoledronate in children[6] and how the choice of bisphosphonate impacts on clinical service costs. This study aimed to assess clinical efficacy of intravenous pamidronate vs zoledronate in children with OI, and provide treatment cost analysis in children with osteoporosis.

Subjects and Methods:

Comparison of efficacy in children with OI

A retrospective clinical service review was undertaken of children with Type I or IV OI aged ≥5 years, who were commenced on treatment with either pamidronate or

zoledronate, over a fourteen year period between January 2001 and December 2014 at Birmingham Children's Hospital, UK. Patients were identified from the departmental OI database. Only patients with dual energy X-ray absorptiometry (DXA) scans prior to commencing treatment were included. As reliable paediatric DXA reference values are only available from age 5 years at our institution, the more severe forms of OI, who commenced treatment at an earlier age, or children without DXA measurements, were excluded. Patients received either generic pamidronate (medac GmbH, Wedel, Germany) administered in courses of 1.5mg/kg over 4 hours/day for 2 days every 3 months, or generic zoledronate (Dr. Reddy's Laboratories Ltd, Telangana, India) as a single dose of 0.05mg/kg over 30min, 6-monthly for a minimum of 2 years.

DXA scans were performed pre-treatment and 1-year post-treatment using either a GE Lunar™ Prodigy or iDXA (GE Medical Systems, Madison, Wisconsin, USA). All scans were analysed using Encore version 15.0 (basic and enhanced). Z-scores for lumbar spine bone mineral apparent density (BMAD, in g/cm^3) were calculated according to our large reference database [7]. In addition, case notes and X-ray images were reviewed to document the number of new long bone and vertebral fractures (VF) sustained in the first two years on bisphosphonate treatment.

Treatment cost analysis

To compare treatment costs, all children with primary (including all types of OI) and secondary osteoporosis treated in our institution with either of the drugs over a 6-year period from 2008, when zoledronate was first introduced, were included. We chose to report treatment courses rather than patient numbers since the latter do not exactly match the former due to variable timing of start and discontinuation of therapy during the year, as well as treatment interruption due to surgery, fractures, non-attendance, etc. Cost analysis was based on drug acquisition cost, nursing and medical time,

equipment and days in hospital per year (8 vs. 2 days/year, for pamidronate vs. zoledronate respectively) as of 2015.

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc. Chicago, IL, USA). Continuous variables are presented as mean (± SD) or medians (interquartile range), as appropriate. Wilcoxon signed-rank test was used for comparing BMAD between the pamidronate vs. zoledronate group.

Results:

Efficacy

Forty patients with Type I or IV OI met the inclusion criteria. By chance, both treatment groups consisted of 20 patients, and did not differ in age [mean age for pamidronate vs zoledronate (9.17y vs 9.7y)], sex distribution [pamidronate 9/11 vs zoledronate 10/10; male/female] and severity of OI [Type I (15), Type IV (5) in each group]. There was no difference in the 2-year pre-treatment prevalent fracture rates in the pamidronate [3.5 ± 1.2 (long bones fractures), 1.8 ± 0.89 (VF)] or the zoledronate group [2.8 ± 1.49 (long bones fractures), 1.75± 1.07 (VF)].

After one year of treatment, lumbar spine BMAD z-scores increased significantly in both groups ($p<0.001$), with no difference between the PAM [+1.67 (1.46-2.21)] and the zoledronate group [+1.75 (1.46-2.00)]. Similarly, incident long bone fracture rate did not differ between pamidronate (3 fractures) and zoledronate groups (2 fractures), with no new VF in the first two years on treatment in both groups. There were no recorded instances of hospitalisation secondary to first phase reaction following the first dose of both pamidronate or zoledronate administration, and no severe adverse reactions resulting in discontinuation of bisphosphonate treatment.

Treatment Costs

The mean number of bisphosphonate treatment courses (pamidronate and zoledronate) for all children with osteoporosis per year between 2008 and 2013 remained constant except for an unexplained increase (35%) in 2012. While pamidronate was the preferred bisphosphonate in 2008 (95% of treatment courses), the trend had reversed by 2013, with the majority of the children receiving zoledronate (93% of courses). (**Figure 1**)

The unit drug acquisition cost by the hospital pharmacy for pamidronate (£ 1.79 per 30mg vial) was comparable to zoledronate (£2.80 per 4mg/5ml vial). Total cost per treatment course per patient was £1157 for pamidronate and £498 for zoledronate. Due to the change in the choice of bisphosphonate, the average cost per treatment course for children with osteoporosis halved from £1128 in 2008 to £540 in 2013 **(Figure 2)**. This change in drug choice has resulted in reduction of annual treatment costs from £174,722 to £84,278, resulting in an annual cost saving of £90,444 (52%) in 2013 compared to 2008.

Discussion:

This study demonstrates comparable BMAD improvement and fracture rates in children with mild to moderate OI treated with pamidronate or zoledronate, and substantial cost savings when choosing zoledronate over pamidronate for treatment of paediatric osteoporosis.

Whilst a previous small study found similar 1-year bone density improvements between pamidronate- and zoledronate-treated children with OI, no data on fracture rates was provided.[6] Here we demonstrate similar long bone and vertebral fracture rates in both drug groups during 2 years of therapy. More severe forms of OI were excluded due to lack of bone density data at initiation of bisphosphonate therapy, and prospective studies are required to compare the long-term efficacy of zoledronate vs pamidronate.

Drug acquisition cost was similar for both drugs. However, the supplies required for administering zoledronate cost 70% less than pamidronate due to the less frequent administration (2 days of zoledronate vs 8 days of pamidronate per year). Also, the supply management and professional service costs, including physician and nursing salaries, preparation and dispensing of medications are significantly lower with zoledronate use due to the fewer treatment cycles per patient per year. From a hospital perspective, the change in choice of bisphosphonate led to major cost savings and creation of substantial bed space for other children requiring day care.

From a patient perspective, fewer treatment courses translate to fewer days off school for children and less time off work for parents/carers, contributing to the reduction in indirect costs. Treatment with zoledronate is also particularly favourable for children with difficult intravenous access and needle phobia.

In conclusion, despite similar drug acquisition costs, the less frequent administration of zoledronate makes it a more favourable economic option for treating paediatric osteoporosis, whilst achieving similar clinical benefits.

Disclosure: The authors declare no potential conflict of interest.

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Figure Legend:

Figure 1: Comparision of annual bisphosphonate treatment courses (a course constitutes 2 days of pamidronate or a single day of zoledronate infusions) for paediatric osteoporosis demonstrates the change in drug choice from pamidronate to zoledronate between 2008 and 2013.

Figure 2: The average cost per treatment course in Great British Pounds over a 6 year period, reflecting the prescribing change from pamidronate to zoledronate.